tobacco smoke in susceptible atopic individuals is not surprising (Speer, 1968; Zussman, 1974; Weber, 1984; Winters, 1985; Cummings et al., 1991). Nevertheless, studies consistently have failed to find any correlation between subjective complaints of sensitivity to tobacco smoke and either skin or serologic tests of immunologic reactivity to tobacco-related antigens (McDougall & Gleich, 1976; Lehrer et al., 1980; Lehrer et al., 1984; Stankus & Lehrer, 1988; Stankus et al., 1988; NRC, 1986; Lebowitz, 1987).

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foundation for such a relationship. In short, the unscientific nature of these "data", the highly questionable validity of the proposed etiologic bases and pathogenetic mechanisms for this condition, and the likelihood that many, if not most, of these individuals suffer from a psychiatric disorder or adhere to a medical subculture or belief system, coupled with the considerable doubt that exists regarding even the basic concept of MCS as a legitimate, defined disease, disorder, syndrome, or nosologic entity (ACP, 1989; Kahn & Letz, 1989; Brodsky, 1987; Terr, 1987; American Academy of Allergy and Immunology, 1986; California Medical Society, 1986; ACOM, 1991), render it, at the very least, premature to consider individuals said to have MCS to be more susceptible to adverse health effects from exposure to ETS in the workplace than the general population.

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IV. INDIVIVUALS WITH "MULTIPLE CHEMICAL SENSITIVITIES SYNDROME"

"Multiple Chemical Sensitivities Syndrome" (MCS) is a term used to describe a poorly defined condition characterized by recurrent symptoms, referable to multiple organ systems, said to occur in response to exposure to a wide variety of chemically unrelated compounds at concentrations far below those established to cause adverse effects or even produce noxious effects on an irritative or immunologic basis in the general population (Cullen, 1987; Simon et al., 1990; Terr, 1987; American College of Physicians, 1989; Terr, 1986; Bascomb, 1989; Black et al., 1990). Other terms used to describe this condition include: Environmental Illness; Environmentally Induced Disease; Chemical Hypersensitivity Syndrome; Cerebral Allergy; Chemically Induced Immune Dysregulation; Twentieth Century Disease; Total Allergy Syndrome; Ecologic Illness; and Food and Chemical Sensitivities (ACP, 1989).

Just as no single term has been used to describe this condition, it also has no single accepted definition, uniform terminology or nomenclature (Bascomb, 1989). Moreover, despite the pathogenetic implications of some of the terms that have been applied to this condition, considerable uncertainty exists regarding pathogenetic mechanisms, criteria for diagnosis, and modes of therapy. These uncertainties have created much doubt in

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necessarily be adverse. Finally, no evidence exists that any therapeutic drug or medication in any way alters an individual's susceptibility or sensitivity to ETS, adversely or otherwise.

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> fear of adverse effects of body effluvia once dominated such perceptions, fear of environmental tobacco smoke now dominates.

* * *

> The relative health threats.....may be quite the opposite of the residents' impressions. In the realm of odors and ventilation, however, any perception of a threat counts heavily. The layman may not know that bad smelling things are not necessarily dangerous (unless eaten) and that neutral or even good smelling things may in fact be dangerous.

> Many people now perceive smoky air as a threat to health. The motivation to control it will therefore derive largely from this perception, much as the motivation to control body odor once derived from fear of its health impact.

Irritation of the eyes and mucous membranes of the nose and throat has both subjective and objective aspects. Unlike annoyance (with which it may be linked, however), irritation can be measured using objective parameters, the most widely used of

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Kahn & Letz, 1989; Cullen, 1987; Committee on Environmental Hypersensitivities, 1985; Bascomb, 1989; Terr, 1986; Ashford & Miller, 21990;).

The concept of MCS was introduced by a group of nontraditional, alternative medicine practitioners known as "clinical ecologists" or practitioners of "environmental medicine", who have also propounded and put forth a number of theories of pathogenesis. These theories propose that adverse effects from synthetic chemicals and/or other common environmental substances (including the ubiquitous fungus, Candida albicans, normally resident in the gastrointestinal tract) can result from exposures far lower than can be explained by accepted pathophysiologic, including immunologic, mechanisms; that immune system damage and "dysregulation" can result from such low-level exposures; that some individuals exhibit "hypersensitivity" to many, if not most or all, synthetic chemicals, as well as to a variety of other ubiquitous substances, involving mechanisms other than conventional immunologic reactions; and that resultant symptoms involving multiple organ systems, but without demonstrable pathologic lesions or specific laboratory abnormalities can occur in these individuals (Bell, 1982; Dickey, 1976; Randolph, 1962; ACP, 1989; Kahn & Letz, 1989; Terr, 1987; Bascomb, 1989; Levin and Byer, 1987).

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the scientific medical community regarding whether MCS is a legitimate physical or pathophysiological disorder or diagnostic entity (Bascomb, 1989; ACP, 1989; Stewart et al, 1985; Brodsky, 1983; Simon et al., 1990; Terr, 1987; Terr, 1986; Terr, 1989; Black et al, 1990; Brodsky, 1987; Schottenfeld, 1987; Kahn & Letz, 1989; American Academy of Allergy and Immunology, 1986; California Medical Society, 1986).

As indicated previously, individuals said to have this condition usually complain of recurrent episodes of a variety of symptoms and/or various chronic symptoms referable to multiple organ systems. Many of these symptoms are nonspecific, neuropsychiatric or constitutional in nature, and are said to be precipitated by exposure to a wide variety of chemically unrelated common environmental substances, including, among others: petroleum products and byproducts; volatile organic compounds (VOC's); synthetic fabrics; foods; food additives; tobacco smoke (including ETS); formaldehyde; perfumes, colognes and deodorants; household and other cleaning products and detergents; plastics; newsprint; vehicle exhaust; fungal and other biological products and agents; and drycleaning chemicals. No corresponding objective physical findings and no conistent laboratory abnormalities or tests of physiologic, biochemical, immunologic or other biologic function have been shown to correlate either with symptoms or with the condition (ACP, 1989;

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V. INDIVIDUALS WITH ATOPIC ALLERGY

Like many plants tobacco leaf contains antigens which, when extracted, can stimulate immune responses in experimental animals and humans (NRC, 1986; Becker et al., 1976). Extracts of tobacco smoke also contain antigens that can stimulate immune responses that cross react with tobacco leaf antigens (NRC, 1986; Becker et al., 1976; Becker et al., 1979; Lehrer et al., 1978; Lehrer et al., 1980a; Gleich & Welsh, 1979; Becker et al., 1981). Furthermore, a significant number of individuals (in some studies as many as 50%) with atopic allergy have been reported to react positively to intracutaneous prick tests with tobacco leaf or tobacco smoke extracts. It has also been reported that a similar proportion of such individuals have serologic evidence of IgE antibody directed against tobacco-related antigens on radioallergosorbent (RAST) testing (NRC/NAS, 1986; Zussman, 1974; Becker et al., 1976; Lehrer et al., 1980b; Lehrer et al., 1984; Lehrer et al., 1985); this compares with prevalence rates for such reactions of 5 - 6% in nonatopic subjects (various Lehrer et al. refs -to be inserted).

In light of this, that it has been suggested that a number of complaints putatively attributable to ETS exposure, such as eye and upper respiratory "irritation", as well as exacerbations of asthma, may be related to IgE-mediated allergic reactions to

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Clinical ecologists have also developed and championed a number of tests for the diagnosis of MCS, including "provocation-neutralization" testing, along with a number of therapeutic modalities including chemical-exposure avoidance, special diets, vitamin and mineral supplements, drug therapy, and so-called "neutralization" therapy (Green, 1974; Lehman, 1980; Morris, 1969; Lee et al., 1969; Rinkel, 1964; Willoughby, 1965; Warren, 1978; Rea et al., 1978; Randolph and Moss, 1980; Bell, 1982; Rinkel et al., 1950; Crook, 1984; Kalin, 1971; Rapp, 1978; Golbert, 1971; Ashford & Miller, ? 1990; Ashford & Miller, 1989; Randolph, 1987; Rogers, 1989).

Both the concept of MCS and the precepts, diagnostic methods, and therapy espoused by clinical ecologists have been found not to meet accepted scientific criteria (Terr, 1989; Van Metre, 1983; Health Care Financing Administration, 1983; American Academy of Allergy and Immunology, 1981; American Academy of Allergy and Immunology, 1986; California Medical Association, 1986; Terr, 1986; ACP, 1989; Kahn & Letz, 1989). Controlled studies addressing immunologic abnormalities, clinical features, diagnostic tests and therapeutic modalities have found no credible, objective support for the various etiologic and pathogenetic mechanisms involving immune system damage/"dysregulation" said to occur in MCS "sufferers" nor have

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disorders, depression, and anxiety disorders, are extremely common in such individuals and may play a pivotal role in the pathogenesis of their symptoms (Terr, 1986; Black et al., 1990; Terr, 1989; Simon, 1990; Stewart et al., 1985; Schottenfeld, 1987; Bolla-Wilson et al., 1988; Rosenberg et al., 1990; Staudenmayer & Selner, 1990; Shusterman et al., 1988). Evidence also suggests that, at least in some patients, the condition represents a "subculture" or belief system as opposed to either a physical or a psychiatric disorder (Brodsky, 1983; Brodsky, 1987; Kahn & Letz, 1989). In this regard, a number of active "environmental illness" support groups publish newletters, lobby for legislation and regulatory action, and attempt to attract media attention. In addition, a number of attorneys actively pursue toxic tort and workers compensation litigation alleging that MCS is caused by or otherwise relates to various occupational and environmental exposures (Kahn & Letz, 1989; Marshall, 1986; Kahn, 1987; Barinaga, ?1991; Cornfeld & Schlossman, 1989).

As noted above, exposure to tobacco smoke, including ETS, has been included among the various exposures alleged to precipitate symptoms or perpetuate chronic illness in individuals said to suffer from MCS. However, the only support offered for this contention are subjective reports lacking objective verification; no acceptable scientific studies provide any

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workers (Federal Register, 1991). In the case of annoyance, whether this is indeed the case is extremely difficult to determine.

Annoyance, as noted above, is largely a subjective phenomenon with few, if any, reliable objective correlates and attitudinal, emotional and psychogenic factors clearly can affect its threshold. Reports of studies on annoyance have primarily been based on questionnaires or other subjective indicies. For example, Cummings et al. (1991) reported that individuals with a history of atopy or respiratory illness are more "sensitive" to the acute effects of ETS exposure than are individuals without such a history but "reactions to ETS" were assessed solely on the basis of the subjects' reports of "how much it bothers them to be exposed to other people's tobacco smoke" and their subjective indications of "whether they typically experience symptoms when exposed to ETS", without any objective verification of these reports. Furthermore, as the authors themselves note, their selection of "a sample of volunteer subjects from a cancer screening clinic" raises serious questions about the validity and significance of their results and conclusions. Similar reservations apply to reports of increased "sensitivity" to tobacco smoke among individuals with the so-called MCS syndrome, discussed elsewhere in this paper, who have subjective symptoms only, without objective physical or laboratory correlates. In

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VI. INDIVIDUALS WITH POSSIBLY HEIGHTENED NONSPECIFIC (NONALLERGIC) SENSITIVITY TO EYE AND/OR UPPER RESPIRATORY IRRITATION

In poorly ventilated areas, ETS can both annoy and irritate the eyes and mucous membranes of the upper respiratory tract (Surgeon General, 1986; NRC, 1986; Weber & Grandjean 1987; Weber, 1985; Muramatsu et al., 1983; Weber et al., 1976; Weber et al, 1979a & b; Weber & Fischer, 1980; Weber, 1984; Cain, 1987; Cain, 1979; Cain et al., 1983; Cain et al., 1986; Clausen et al., 1984; Clausen et al., 1985; Bascomb et al., 1991).

Annoyance caused by ETS, however, is largely a subjective phenomenon. It appears to be closely linked to odor perception, and is associated primarily with the gas phase of tobacco smoke (Cain, 1987; Cain, 1979; Cain et al., 1983; Clausen et al., 1984; Clausen et al., 1985; Muramatsu et al., 1983; Weber & Grandjean, 1987; Nishida et al., 1990; Weber, 1985; Lebowitz, 1987;). The threshold for odor perception and annoyance from ETS is considerably lower than that for irritation (Lebowitz, 1987; Weber, 1984; Weber, 1985; Weber & Grandjean, 1987), is lower for nonsmokers than smokers, and is lower for females than males (Cain, 1987; Cain et al., 1983; Clausen et al., 1985). Potentially relevant to the workplace, data from several studies suggest that visitors to an area have a somewhat lower threshold

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fashion, dependent, in part, on levels of ventilation and relative humidity. Evidence also suggests that attitudinal, emotional and psychogenic factors play a role in such reactions, at least in some individuals. ~~In short,~~ it has not been convincingly demonstrated, however, that certain individuals in the workforce are particularly hypersensitive or susceptible to such effects on any physiological basis.

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several reasons for this increased nasal responsiveness in ETS-S subjects, including differences in nasal geometry and nasal lining. They also suggest that the increased nasal resistance (as well as rhinorrhea and nasal congestion) may result from vasodilation and increased vascular permeability. However, increased vascular permeability appeared unlikely to have occurred since nasal lavage did not reflect transudation of plasma proteins.

Although these findings are provocative, the high level of tobacco smoke exposure to which the subjects were exposed (CO level of 45 ppm) raises questions about their significance and their applicability to realistic conditions of workplace exposure. While their data includes both objective measures (nasal resistance, pulmonary function) and subjective parameters, a psychogenically mediated reaction in the ETS-S subjects cannot be excluded, particularly in light of the distinctive odor and likely nonspecific eye irritation that would be associated with such high levels of tobacco smoke (citations to be inserted).

In summary, ETS can cause annoyance, most likely related to odor perception, and eye and upper respiratory irritation, most likely on a nonspecific, nonimmunologic irritant basis. Such responses to ETS exposure occur in a dose (concentration) related

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from exposure to ETS. Additionally, no data in the literature suggests that the interaction between ETS components and medications alters pharmacodynamic or immunologic responses.

In the absence of data, some speculation on whether ETS components can influence metabolism of medications, thereby increasing or decreasing the blood and tissue levels achieved for the drugs is warranted. Hypothetically, this could occur for either of two reasons. First, any drug taken orally must first pass through the gastrointestinal mucosa and the liver before entering the systemic circulation, and if ETS components caused an increase in drug metabolizing enzymes in those tissues this could reduce the amount of drug ultimately reaching the system. Second, if ETS caused an increase in the amount of drug metabolizing enzymes in the liver primarily, the amount of time that the drug circulates could be reduced.

The effects of other drugs and nutritional and environmental agents on drug metabolism are well known. A plethora of agents can increase or decrease drug metabolism. It is particularly relevant that pyrolysis products -- such as those found in fried or charcoal-broiled meat and fish -- can increase drug metabolism (citations to be inserted). This is believed due, in part, to the polycyclic hydrocarbon benzo[a]pyrene, which is found in most, if not all, pyrolysis products of organic materials

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intense in the ETS-S group. The ETS-S group, but not the ETS-NS group, reported significant increases in nasal congestion, headache, chest discomfort or tightness and cough following exposure. Twenty minutes after ETS exposure, the ETS-S group but not the ETS-NS group exhibited 2-fold increases in nasal resistance.

Pulmonary function changes were small (2%) but statistically significant for FVC, FEV_{1}, and FEF_{25-75} in the ETS-S group after smoke exposure but were considered by the authors to be clinically insignificant. Intra-individual differences in these parameters of less than 5-10% (and in some cases even less than 15-20%) under such study conditions are considered to be within the range of normal intra-test variability and neither physiologically nor clinically significant (Bates, 1989; Miller, 1986). No significant effects were observed on histamine, albumin, kinin, or TAME-esterase activity in nasal lavage.

According to the authors of this study, the data provide objective evidence of increased responsiveness in historically tobacco smoke sensitive nonasthmatic subjects of the upper respiratory passages from ETS, without clinically significant changes in pulmonary function. They further suggest that this nasal response in ETS-S subjects is not IgE-mediated because of the lack of effect on intranasal histamine. The authors propose

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VIII. ELDERLY INDIVIDUALS

In comprehensive reviews of the literature, the National Research Council and the Surgeon General (NRC, 1986; Surgeon General, 1986) revealed no data with respect to adverse effects of ETS exposure, including respiratory and cardiovascular effects, on the elderly.

Subsequent reviews in this country and abroad have also reported that no data exists in this area (Frogatt, 1988; EPA, 1990; other citations to be inserted - e.g., Australia, etc.), and a computer assisted search of the scientific literature in preparation of this document confirms this. The only exception is the Polish study by Jedrychowsk et al. (19901,b), which is discussed in detail in another section of this document, and which provides little, if any, compelling evidence to support such a proposition.

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under experimental conditions (various Weber studies - refs to be inserted) are more typical of a nonspecific, nonimmunologic irritant effect and not at all consistent with an allergic reaction (citations to be inserted).

Bascomb et al. (1991) recently examined the physiologic basis for claimed smoke sensitivity in nonasthmatic subjects. Subjects were classified either as ETS sensitive (ETS-S) or ETS insensitive (ETS-NS) on the basis of their subjective reports of one or more rhinitis symptoms (congestion, rhinnorhea, or sneezing). While both ETS-S and ETS-NS subjects reported histories of eye irritation from ETS exposure, the perception of irritation was quantitatively higher in the former. Additionally, ETS-S subjects also exhited a more than two-fold higher incidence of skin test atopy to common environmental allergens than ETS-NS subjects.

Posterior nasal resistance, spirometry, nasal lavage constituents and subjective quantitation of symptoms were measured in both groups following exposure to 15 minutes of high levels of ETS (CO level of 45 ppm) and the data obtained compared to similar data obtained following a 15 minute exposure to clean air. Both groups reported increases in the perception of odor and irritation of the eyes, nose and throat after tobacco smoke exposure, with nose and throat irritation being reported as more

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It is quite possible that perception (possibly related to odor detection and annoyance), suggestion, and other emotional and psychological factors affect both subjective complaints and objective physiological correlates of eye and upper respiratory irritation. These same factors clearly have been demonstrated to affect complaints of shortness of breath and cough and clinical and physiological correlates in asthmatics, to affect symptoms and clinical findings in other respiratory conditions, and to influence nonspecific or constitutional symptoms and findings in other exposures, e.g., SBS (Horton et al., 1978; Jones et al., 1976; Luparello et al., 1968; McFadden et al., 1969; Philipp et al., 1972; Spector et al., 1976; Weiss et al., 1970; Spitzer et al., 1987; Burns & Howell, 1969; Rosser & Guz, 1981; Brashear, 1987; Agarwal & Sethi, 1978; Thompson & Thompson, 1985; Dales et al., 1989; McKay et al., 1989; Bardana et al., 1988; Skov et al., 1989). The data in this regard relative to eye and upper respiratory irritation, however, are limited and controversial (Cain, 1987; Winneke et al., 1990; Urch, 1988).

Some investigators have suggested that certain individuals or groups may be "hypersensitive" to the annoyance and/or irritation effects of exposure to ETS (Lebowitz, 1987; Winters, 1985; Hulka, 1990; NRC/NAS, 1986; Weber, 1984) and this question is, in fact, raised by OSHA relative to potentially susceptible

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for odor perception and annoyance from ETS than individuals who occupy the area for a longer period of time (Cain, 1987; Clausen et al., 1985; Cain et al., 1983; Cain et al., 1986; Muramatsu et al., 1983).

Additionally, emotional and psychogenic factors may affect ETS odor perception and annoyance and may reflect, at least to some extent, pre-existing, more generalized reaction tendencies as opposed to specific environmental conditions (Winnecke et al., 1984; Cain, 1987; Winnecke et al., 1990). A similar phenomenon has been reported with respect to other environmental exposures, such as the Sick Building Syndrome (SBS) and other responses to various exposures, including shortness of breath and airflow obstruction in asthmatics (Skov et al., 1989; Colligan, 1981; Robertson et al., 1985; Dales et al., 1989; Urch et al., 1988; Horton et al., 1978; Jones et al., 1976; Luparello et al., 1968; McFadden et al., 1969; Philipp et al., 1972; Spector et al., 1976; Weiss et al., 1970; Spitzer et al., 1987; Burns & Howell, 1969; Rosser & Guz, 1981; Brashear, 1987; Agarwal & Sethi, 1978; Thompson & Thompson, 1985; Bardana et al., 1988; McKay et al., 1989). As noted by Cain (1987):

> People assess the quality of the air indoors primarily on the basis of its odor and on their perception of associated health risk. Whereas

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short, it has not been demonstrated by any reasonable objective criterion that any individuals truly are hypersensitive to the annoyance effects of ETS on anything other than a psychogenic basis.

As indicated previously, tobacco smoke and tobacco leaf contain antigens which cause cutaneous and serologic immunological reactions in a significant percentage of atopic and, in a much lower percentage of nonatopic, individuals (Speer, 1968; Zussman, 1974; Becker et al., 1976; Becker et al., 1979; Lehrer et al., 1978; Gleich & Welsh, 1979; Lehrer et al., 1984). Furthermore, a significant number of individuals with a history of atopy may report eye and upper respiratory irritation from ETS. This has led to speculation that atopics are more susceptible to such irritation by virtue of an immunologic hypersensitivity reaction (Speer, 1968; Zussman, 1974; Weber, 1984; Winters, 1985; Hulka, 1990; Cummings et al., 1991). However, this hypothesis has not been supported by studies that have consistently failed to demonstrate any correlation between subjective complaints of tobacco smoke sensitivity and objective cutaneous and serologic tests of immunologic reactivity to tobacco-related antigens (McDougall & Gleich, 1976; Lehrer et al., 1980; Lehrer et al., 1984; Lehrer et al., 1986; Stankus & Lehrer, 1988; Stankus et al., 1988). Furthermore, the dose response characteristics of irritant reactions to ETS exposure

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of the five subjects). Each individual was given a pre- and post-exposure oral dose of theophylline. No changes in theophylline disposition were observed. Clearly, this was a short-term exposure, but five days is generally adequate for enzyme induction when an adequate dose is applied. This study suggests that ETS does not play a role in the induction of drug metabolizing enzymes.

The Request for Information appears to presume that the effect, if any, of ETS exposure on drug disposition is an adverse effect (Federal Register, 1991). This is not necessarily the case. Genetic polymorphism among humans for drug metabolizing enzymes is common; it is understood that dosage variations might be necessary among patients. The fact that two individuals might not respond in the same way to the same dose need not be a limiting factor. Individualizing drug dosing regimens is a desirable approach to pharmacotherapy.

In summary, no evidence suggests that ETS exposure affects the pharmacology or pharmacokinetics of any therapeutic drug or medication. Furthermore, while such an effect may be theoretically qualitatively plausible, by extrapolating from what is known about active smoking and the effects of other pyrolysis products, it does not appear to be quantitatively plausible. In addition, even if such an effect were to occur, it would not

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which appears to be eye blink rate (Weber-Tschopp et al., 1976; Muramatsu et al., 1983; Weber & Grandjean, 1987; Weber, 1985; Weber, 1984; Weber et al., 1976; Weber et al., 1977 a & b; Weber et al., 1979; Weber & Fischer, 1980). Studies in which such measurements have been conducted report irritation to be associated primarily with the particulate phase of tobacco smoke (Weber & Grandjean, 1987; Weber, 1985), although some data suggest the possibility of a more significant role for gas phase components (Lee, 1990; Lebowitz, 1987; Hulka, 1990). Like annoyance and odor perception, irritation from ETS is a dose (concentration) related occurrence that exhibits a threshold and a no-effect level, although the threshold for irritation is significantly higher than that for annoyance/odor perception. There are differences in temporal dynamics between the two phenomena as well (Weber, 1985; Weber & Grandjean, 1987; Cain, 1987; Winneke et al., 1984; Winneke et al., 1990; Lebowitz, 1987). The threshold and prevalence of irritation from ETS, like many other air pollutants, appears to be related to the levels of ventilation and, possibly, relative humidity, although only limited data are directly applicable to the latter (Cain, 1987; Cain et al., 1986; Weber et al., 1979; Weber, 1984; Weber, 1985; Weber & Grandjean, 1987; Weber & Fischer, 1980; Muramatsu et al., 1983; Bardana et al., 1988; Andersen et al., 1974; Anderson et al., 1982; Baetjer, 1968; Hahn et al., 1984; Melia et al., 1982; Sheppard et al., 1984; NRC/NAS, 1986; Kerka & Humphreys, 1956).

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VII. INDIVIDUALS TAKING VARIOUS THERAPEUTIC DRUGS & MEDICATIONS

OSHA cites Calabrese (1978) for the proposition that "[s]ome people may develop an increased sensitivity to chemical pollutants, such as found in [E]TS, during ... treatment with certain medications" (Federal Register, 1991). The basis for this proposition is unclear but it seems to imply (1) medications can act on the body in some way to make the individual more susceptible to the harmful effects of environmental pollutants; and (2) environmental pollutants can alter the body's responses to medication.

Feasible interactions between pollutants can either be pharmacodynamic, immunologic, or pharmacokinetic. Pharmacodynamic interactions are those in which the actual biological activity of one agent adds to, potentiates, or antagonizes the activity of the other. Immunologic interactions are those in which one agent influences the immunogenicity of the other. Pharmacokinetic interactions are those in which one agent influences the blood or tissue level of the other by affecting absorption, distribution, metabolism, or excretion of the active substance.

No data in the published scientific or medical literature suggests that any therapeutic drug or medication alters a subject's susceptibility or sensitivity to adverse health effects

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including mainstream tobacco smoke. Clearly, however, a variety of other compounds in pyrolysis products are known inducers of drug metabolizing enzymes.

Active tobacco smoking has been associated with the increased metabolism of a number of drugs, including theophylline, imipramine, pentazocine, and nicotine. This results in large part from stimulation of the cytochrome-P450-dependent mixed function oxidases (MFO); however, not all drugs metabolized via MFO will be influenced by tobacco smoke. Cytochrome P-450 enzymes are polymorphic, some of which are induced by tobacco smoke and some of which are not.

That mainstream tobacco smoke (MS) induces drug metabolism does not necessarily mean that environmental tobacco smoke will do the same. Both qualitative and quantitative differences exist between MS and ETS. The one study where a comparison was made reaches this conclusion (Casto et al., 1990). It is well established that the metabolism of theophylline, a bronchodilator used in the treatment of asthma, is induced by active tobacco smoking; for this reason, the smoker requires a higher dose of theophylline for asthma management than does the non-smoker. Casto et al. (1990) exposed five male non-smokers to tobacco smoke at a level sufficient to increase urinary cotinine concentrations to greater than that usually used as an indication of ETS exposure (greater than twice the indicator level in four

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such studies confirmed the validity of diagnostic studies or therapeutic maneuvers proposed by the clinical ecologists in relation to MCS (Simon et al, 1990; Terr, 1986; Terr, 1987; Kahn & Letz, 1989; ACP, 1989; Jewett et al., 1990; Ferguson, 1990; Koller, 1985; Patterson et al., 1988). It has been demonstrated that the proposed "diagnostic tests", such as "provocation-neutralization", rely entirely on subjective responses, without objective correlates, and that the great majority -- if not all -- of the data relied upon to support both the validity of MCS diagnostic techniques and modalities of treatment is anecdotal and poorly controlled or otherwise flawed, uninterpretable and scientifically unacceptable (California Medical Association, 1986; Kahn & Letz, 1989; ACP, 1989; Terr, 1987; Terr, 1989; American Academy of Allergy and Immunology, 1986; Advisory Panel on Environmental Hypersensitivity, 1986; Salvaggio, 1990; Salvaggio, 1991; Selner & Condemi, 1988; VanArsdel & Larson, 1989).

Scientifically acceptable studies have demonstrated that patients said to have MCS exhibit such a variety of symptoms that it may not even be justifiable to consider the condition as a defined disease, syndrome or nosologic entity (Terr, 1986; Terr, 1989; Black et al., 1990; Simon, 1990; ACP, 1989; Kahn & Letz, 1989). A number of investigators have suggested that psychogenic mechanisms and psychiatric disorders, including somatoform

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